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THE NATURE OF WATER INTOXICATION

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THE NATURE OF WATER INTOXICATION¹

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ABSTRACT

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The paper shows that the water retained in the body during water intoxication and the decrease in inorganic salts in both blood and tissues is considerable. Consequently, one cannot seek the nature of water intoxication directly and simply in water retention in the tissues or in hydremia. On the contrary, it seems more likely that the nature of this intoxication is closely related to the decrease of inorganic salts in the tissues and the high reduction of serum molecular concentration.

Author

1. Introduction

Numerous investigations into water toxicity already exist. Only isolated reports are found regarding the toxic manifestations of excessive water intake. In 1921 Miller and Williams reported that daily administration of 10 liters of water per os in patients suffering from chronic nephritis and hypertonia produced various symptoms, such as increase in blood pressure, headaches, restlessness, vertigo, chills, abdominal distention, vomiting, dyspnea and cramps in the lower extremities. Strange to say, however, the same water dosage did not produce such symptoms in their diabetes insipidus patients. Recently, Rowntree observed that, in Pituitrin treatment of diabetes insipidus patients to whom much water was given, disagreeable symptoms appeared, such as nausea, violent headaches, swelling of the lower eyelids and, in one case, ataxia.

This interesting discovery caused him to undertake animal experiments which established that, in various mammals, hourly gastric administration of 50 cc of water per kg after Pituitrin injection or half-hourly administration of the same amount without injection produced a number of

¹Address delivered at the Congress of the Medical Association in Tokyo, 20 September 1926.

toxic manifestations, particularly cramps suggestive of strychnine poisoning, after the water administered reached a specific amount. He called this syndrome "water intoxication," and assumed, moreover, that it occurred because of equilibrium disturbances during water resorption, assimilation and secretion.

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In his further report he explained the causes of water intoxication coming under consideration, and indeed, these were to be found neither in uremia, eclampsia and epilepsy, nor in repeated stomach probings in water administration, in gastric dilatation and liver injury, nor in resorption of the digestive products and enzyme from the gastrointestinal tract. He finally traced the phenomenon of intoxication back to the disturbance in water-salt balance caused by the idiopathic increase in intracerebral pressure. He adduced no proof for this, however. With this state of affairs, it seemed eminently desirable to analyze this intoxication accurately and consider it in more detail. Since May 1925, therefore, on the assumption that water intoxication is based on tissue desalinization, I carried out the following experiments under the advice and guidance of Professor R. Inada. When I had almost completed the work at hand, Underhill and Sallick reported several investigations into water intoxication, which they believed confirmed Rowntree's hypothesis. However, they only performed a few chemical investigations.

2. Water Intoxication in General

As experimental animals we used 67 adult male rabbits, to whom 50 cc of room-temperature tap water per kg was administered gastrically every half-hour. As soon as the water reached a specific level, the animals exhibited various symptoms such as asthenia, restlessness, polyuria, pollakiuria, diarrhea, salivation, dyspnea, tremors, etc. Other mammals in Rowntree's experiments also exhibited nausea and vomiting, which were absent in our rabbit research. Finally, the animals were seized with cramps, whereupon the real investigations began. Determination of some substances was made during the earlier intoxication period.

Aggregate water administration, total quantity of water administered in comparison with body weight, and elapsed time prior to appearance of cramps varied somewhat in individual cases, to be sure, but in the main they were similar, as is evident from the following table.

a. Aggregate water administration:

Number of cases	Percent
6	11.1
7	53.3
8	22.2
9	11.1
10	2.2

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b. Total quantity of water administered in comparison with body weight prior to onset of cramps:

	Percent
Upper limit	48
Lower limit	30
Mean value for all cases	36

c. Elapsed time to occurrence of cramps:

Shortest time	3 hr 3 min
Longest time	5 hr 10 min
Mean	3 hr 46 min

The cramps thus appeared after some 7-8 administrations of water and 3-1/2-4 hr after the experiment began, when the total quantity of water administered reached approximately one-third body weight.

The pertinent chemical-substance determination methods are specified in their corresponding sections.

3. Blood Research in Water Intoxication

The following chemical and morphological investigations were performed on blood. The blood used in the research was always collected in drops from external-ear veins of the rabbit.

a) Inorganic salts

Rusznayak's method was used for sodium chloride determination; sodium, potassium and calcium were determined according to Kramer-Tisdall. The Denis method was used for magnesium, and phosphorus determination was made according to Bell-Doisy. Sodium chloride, sodium, potassium, calcium and magnesium content in the serum and phosphorus content in the plasma immediately after the onset of cramps was always compared with that obtaining prior to water administration.

Control experiments were performed to establish whether taking as little as 5 to 8 cc of blood affected the blood-content of the various inorganic salts. Five to eight days before the actual experiment 5 to 8 cc of blood was taken twice, at an interval of 4 to 4-1/2 hr, from the animals later used in the experiment and the inorganic salts in each blood sample determined and compared with each other. It was thus established that withdrawal of 5-8 cc of blood had no perceptible effect on inorganic salt content.

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In five control experiments the percentual change in sodium chloride content of the blood taken later relative to that taken earlier fluctuated between -1.1 percent (6 mg/dl) and +2.0 percent (12 mg/dl), averaging

-0.5 percent, the minus signifying a decrease and the plus an increase. Such a small percentage variation, of course, lies within experimental limits of error. In all 11 actual experiments, on the other hand, with the appearance of cramps, sodium chloride blood-content decreased to a remarkable degree. The percentual decrease in sodium chloride content thus fluctuated between 16.5 percent (78 mg/dl) and 29.8 percent (153 mg/dl) and averaged 22.5 percent. All the research results are compiled in Table 1.

Table 1. Sodium Chloride

	Rabbit No.	Date	Body weight (g)	Total water volume (cc)	Time (hr/min)	Before (mg/dl)	After (mg/dl)	Difference (%)	Mean percentage
Control	7	4. VIII.	1935		4.30	575	570	- 0.9	+ 0.5%
	8	4. 1925	1980		4.15	561	555	- 1.1	
	9	5.	1730		4.40	554	568	+ 2.0	
	10	8.	2570		4.35	521	530	+ 1.7	
	55	18. I. 1926	2210		4.20	537	540	+ 0.6	
Water intoxication	7	10. VIII.	1935	855	4.47	513	360	- 29.8	-22.5%
	8	10. 1925	1990	665	4. 1	557	418	- 25.0	
	9	11.	1700	595	3.30	570	476	- 16.5	
	10	14.	2600	900	3.27	492	375	- 23.8	
	11	14.	1975	945	5.10	495	370	- 21.2	
	12	20.	3020	1050	3.15	511	380	- 25.6	
	13	21.	1720	760	4.15	461	383	- 16.9	
	21	8. IX.	2400	840	3.27	534	395	- 26.0	
	23	10.	2260	770	3.33	548	430	- 21.5	
	24	15.	2120	840	3.50	535	432	- 19.3	
	26	18.	2175	735	3.25	562	442	- 21.4	

The percentual difference in sodium content between the first and last blood-taking in five control experiments fluctuated between -1.8 percent (6 mg/dl) and -4.6 percent (15 mg/dl), averaging -3.4 percent. Here, too, this small variation must not be regarded as a true change. In six actual experiments, however, the sodium content decreased to a more or less high degree and showed a fluctuation between -13.6 percent (43 mg/dl) and -20.6 percent (73 mg/dl). The mean value was -17.3 percent. Individual experiments are reproduced in Table 2.

Five control experiments were performed with regard to potassium content. Its percentual change between last and first blood-takings fluctuated between -5.4 percent (0.9 mg/dl) and +4.1 percent (0.6 mg/dl), averaging -1.8 percent. This range is indeed rather large, but does not exceed the limits of error. In seven actual experiments the decrease in potassium content varied between 10.6 percent (2 mg/dl) and 32.3 percent (6 mg/dl), averaging 18.4 percent. Details appear in Table 3.

Table 2. Sodium¹

	Rabbit No.	Before (mg/dl)	After (mg/dl)	Difference, percent	Mean percentage difference, percent
Control	7	309	300	- 3.9	- 3.4
	8	341	335	- 1.8	
	9	300	293	- 2.3	
	10	377	361	- 4.2	
	55	327	312	- 4.6	
Water intoxication	7	303	260	-14.2	-17.3
	8	316	273	-13.6	
	9	355	282	-20.6	
	10	390	323	-17.2	
	11	395	319	-19.2	
	12	311	252	-19.0	

Table 3. Potassium

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	Rabbit No.	Before (mg/dl)	After (mg/dl)	Difference, percent	Mean percentage difference, percent
Control	7	14.4	13.8	- 4.1	- 1.8
	8	17.9	18.1	+ 1.1	
	9	20.3	19.3	- 4.9	
	10	14.8	15.4	+ 4.1	
	55	16.8	15.9	- 5.4	
Water intoxication	7	17.1	14.6	-14.7	-18.4
	8	18.8	16.8	-10.6	
	9	18.6	12.6	-32.3	
	10	15.2	14.0	- 7.9	
	11	20.2	16.3	-19.3	
	12	21.0	15.3	-27.1	
	15	18.0	14.9	-17.2	

¹Where date, body weight, total quantity of water and time are not indicated in the tables, they appear in a previous table or, in some cases, in a subsequent one. In this connection, the same number indicates the same rabbit.

In five control experiments the calcium content of the second blood-taking varied only slightly from that of the first, except in one case, where it increased about 8.1 percent (0.9 mg/dl). Mean value of the percentage change was +1.3 percent. In 13 actual experiments the calcium content varied between 13.6 percent (1.6 mg/dl) and 25.4 percent (3 mg/dl), averaging -19.2 percent, as is evident in Table 4.

Table 4. Calcium

	Rabbit No.	Before (mg/dl)	After (mg/dl)	Difference, percent	Mean percentage difference, percent
Control	7	13.6	13.7	+ 0.7	+ 1.3
	8	11.7	11.5	- 1.7	
	9	11.1	12.0	+ 8.1	
	10	13.3	13.0	- 2.3	
	55	12.7	12.9	+ 1.6	
Water intoxi- cation	8	13.5	10.1	-25.2	-19.2
	9	11.8	9.9	-16.1	
	10	13.3	10.3	-22.6	
	11	12.1	10.0	-17.4	
	12	13.9	10.7	-23.0	
	13	11.9	10.1	-15.2	
	15	11.8	8.8	-25.4	
	18	14.2	11.3	-20.4	
	23	14.0	10.7	-23.6	
	24	13.3	11.2	-15.8	
	26	11.8	10.2	-13.6	
	27	12.7	10.8	-15.0	
	28	12.0	10.1	-15.8	

Magnesium content behaved similarly. Thus in five control experiments its percentual change varied between +1.1 percent (0.02 mg/dl) and -5.5 percent (0.09 mg/dl), averaging -2.4 percent. In seven actual experiments magnesium blood-content decreased very sharply with the onset of cramps; indeed, it decreased between 33.7 percent (0.61 mg/dl) and 65.3 percent (0.79 mg/dl), with the exception of one case in which, conversely, it increased about 9.9 percent (0.1 mg/dl). The cause of this contrary finding remains a mystery. Mean value of the percentage change in magnesium content was -38.3 percent. More precise results appear in Table 5.

It should be mentioned here that magnesium content in the serum is by nature very insignificant as compared with other salts, and, consequently, the technical limit of error in magnesium content determination is all the greater when it decreases in any way.

Table 5. Magnesium

	Rabbit No.	Date	Body weight (g)	Total water volume (cc)	Time (hr/min)	Before (mg/dl)	After (mg/dl)	Difference (%)	Mean percentage difference
Control	18	27.VIII.1925	2400		4.0	1.62	1.60	- 1.2	- 2.4%
	24	7.IX.	2150		4.10	1.83	1.85	+ 1.1	
	26	18.	2180		4.5	1.70	1.64	- 3.5	
	56	18.I. 1926	2120		4.10	1.35	1.31	- 3.0	
	57	18.	2200		4.5	1.64	1.55	- 5.5	
Water intoxication	15	27.VIII.1925	2335	805	3.55	1.21	0.42	- 65.3	- 38.3%
	18	3.IX.	2415	720	3.10	1.81	1.20	- 33.7	
	23	10.	2260	770	3.33	1.01	1.11	+ 9.9	
	24	15.	2120	840	3.50	1.76	0.87	- 49.4	
	26	21.	2175	735	3.25	1.73	1.13	- 34.7	
	27	26.	2030	700	3.30	1.70	1.00	- 41.2	
	28	28.	2130	735	3.10	1.67	0.89	- 46.7	

In five control experiments the inorganic phosphorus content decreased almost to an equally great degree in the second blood-taking as compared with the first; the mean percentage decrease was 3.1 percent. In six actual experiments, however, it fluctuated between 13.5 percent (0.4 mg/dl) and 30.0 percent (1.11 mg/dl), averaging 21.2 percent. Exact results appear in Table 6.

Table 6. Phosphorus

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	Rabbit No.	Date	Body weight (g)	Total water volume (cc)	Time (hr/min)	Before (mg/dl)	After (mg/dl)	Difference (%)	Mean percentage difference
Control	29	26.IX. 1925	2030		4.10	3.02	2.95	- 2.3	- 3.1%
	30	28.	2690		4.15	3.40	3.30	- 2.0	
	31	29.	2310		4.5	3.85	3.71	- 3.6	
	32	29.	2180		4.20	3.41	3.30	- 3.2	
	56	18.I. 1926	2120		4.10	3.52	3.40	- 3.4	
Water intoxication	29	2.X. 1925	2045	900	4.20	2.97	2.37	- 19.5	- 21.2%
	30	2.	2675	910	3.40	3.70	2.59	- 30.0	
	31	6.	2300	690	4.0	3.90	3.06	- 21.5	
	32	7.	2190	770	4.5	3.20	2.80	- 13.5	
	56	25.I. 1926	2120	735	3.35	3.62	2.91	- 19.6	
	57	25.	2200	770	3.25	3.21	2.48	- 22.7	

b) Blood protein and albumin-globulin ratio

Control experiments were carried out here in the manner described above. In five control experiments the change in blood-protein content in relation to the initial value fluctuated relatively between +0.1 percent and -1.5 percent or absolutely between 0.01 percent and 0.09 percent with the exception of one case in which it was about 4.5 percent relatively or 0.27 percent absolutely. Mean value was -1.3 percent. In nine actual experiments the percentage decrease in relative fluctuation lay between 15.9 percent and 31.9 percent or between 0.99 percent and 2.16 percent absolutely, except in one case in which it decreased relatively about 9.1 percent or absolutely about 0.67 percent. The mean value was thus -23.5 percent, as is seen in Table 7. According to these results, it can be stated briefly that a sizable decrease in blood-protein content is evident in water intoxication. A considerable hydraemia therefore exists in the blood.

Table 7. Blood Protein

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	Rabbit No.	Before, percent	After, percent	Difference, percent	Mean percentage difference, percent
Control	7	6.05	5.78	- 4.5	- 1.3
	8	5.99	5.90	- 1.5	
	9	5.75	5.76	+ 0.1	
	10	6.93	6.94	+ 0.1	
	55	6.10	6.05	- 0.8	
Water intoxi-	7	6.12	4.92	-19.6	-23.5
	9	6.08	4.27	-29.8	
	10	6.75	4.70	-30.4	
	11	7.35	6.68	- 9.1	
	12	6.77	4.64	-31.9	
	23	6.27	4.84	-23.6	
	26	6.24	5.25	-15.9	
	27	6.08	4.37	-28.1	
	28	6.34	4.90	-22.7	

Although the blood-protein content decreased significantly, the albumin-globulin ratio showed no substantial change. As is evident from Table 8, the globulin only decreased about 2.4 percent to 5.7 percent, while the albumin increased proportionately. With such a small increase or decrease, of course, one cannot speak of the change in albumin-globulin ratio.

Table 8. Albumin and Globulin in Blood Protein

Rabbit No.	Date	Body weight (g)	Total water volume (cc)	Time (hr/min)	Before		After	
					Blood Protein %		Blood Protein %	
					Albumin %	Globulin %	Albumin %	Globulin %
63	12. IV. 1926	2260	880	3.35	68.6	31.4	74.3	25.7
64	12.	2450	840	4.15	64.2	35.8	52.5	47.5
65	14.	2170	840	4.16	75.6	24.4	78.0	22.0
66	14.	2270	770	3.5	67.8	32.2	71.7	28.3
67	14.	2150	735	3.25	81.5	18.5	65.5	34.5
					70.2	29.8	73.9	26.1

c) Residual nitrogen

The blood was proteolyzed by trichloroacetic acid for determination of residual nitrogen. This decreased slightly in water intoxication, as is shown in Table 9.

Table 9. Residual Nitrogen

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Rabbit No.	Date	Body weight (g)	Total water volume (cc)	Time (hr/min)	Before (mg/dl)	After (mg/dl)
39	18 Oct 1925	2080	700	3.55	46	39
40	18 Oct 1925	2040	700	3.23	49	46
41	20 Oct 1925	2185	756	3.43	53	47

d) Blood water-content and solid matter

Solid matter in the blood was determined three times in each experiment: before the experiment, in the middle of it, and immediately after the onset of cramps. About 1-2 cc of blood was taken each time, and used to determine the solid matter. It showed that this decreased gradually with intoxication. Thus in five experiments it varied between 17.7 percent and 20.5 percent (mean 18.5 percent) before the experiment, and between 14.4 percent and 17.2 percent (mean 15.8 percent) after the onset of cramps. The mean percentage decrease in solid matter with the onset of cramps in comparison with the initial value was thus 14.6 percent. Correspondingly, blood water-content, on the contrary, increased from 81.5 percent before the experiment to 84.2 percent with the onset of cramps. Table 10 shows this relation.

Table 10. Solid Matter in the Blood

Rabbit No.	Before			Midway			After			Decrease in percentage composition of solid matter
	Weight of blood (g)	Weight of solid matter (g)	Percent of solid matter	Weight of blood (g) (hr/min)	Weight of solid matter (g)	Percent of solid matter	Weight of blood (g)	Weight of solid matter (g)	Percent of solid matter	
33	1.0867	0.1917	17.6	1.3025(2.30)	0.1975	15.1	0.8276	0.1192	14.4	18.2
34	1.3705	0.2528	18.5	1.3963(3.15)	0.2366	17.0	1.5172	0.2474	16.4	11.4
35	0.7610	0.1401	18.4	1.4936(2.25)	0.2477	17.6	0.4319	0.0695	16.0	13.1
36	2.0788	0.4287	20.5				1.1917	0.2044	17.2	16.1
37	2.4426	0.4309	17.7	1.3458(2.30)	0.2153	16.0	1.8772	0.2858	15.2	14.1
Mean			18.54						15.84	14.58

e) Blood sugar

In five experiments blood-sugar content was assayed three or four times during manifestations of intoxication. This showed that the blood-sugar level, without occurrence of glycosuria, gradually rose a little in the course of water intoxication. For example, in a pronounced case it was about 0.048 percent higher with the onset of cramps than before the experiment. Complete results appear in Table 11.

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Table 11. Blood Sugar

Rabbit No.	Date	Body weight (g)	Total water volume (cc)	Time (hr/min)	Before (%)	Midway (%) (hr/min)	After (%)	Increase (%)
33	10.X.1925	2100	840	4.15	0.103	0.119(1.20) 0.122(2.30)	0.143	0.040
34	10.	2090	800	4.55	0.076	0.080(2.0) 0.105(3.5)	0.118	0.042
35	13.	2085	960	4.12	0.082	0.087(1.40) 0.082(3.20)	0.096	0.014
36	14.	2050	720	4.3	0.105	0.131(1.15)	0.153	0.048
37	15.	2150	945	4.15	0.083	0.084(2.30)	0.100	0.017

f) Molecular concentration

It now seemed interesting to know whether and how sharply molecular concentration of the blood serum is lowered in water intoxication, remembering that on the one hand inorganic salt content decreased sharply, while on the other hand blood sugar increased a bit. Determination of the lowering of the freezing point of the serum was therefore undertaken. Here it should be emphasized again that the blood was only collected in drops from external-ear veins, as described above. In control experiments on three animals the freezing-point depression was a uniform -0.74°C , while in three water-intoxicated animals it was -0.60° , -0.61° and -0.60°C respectively, as is shown in Table 12. A sharp decrease is thus noted in serum molecular concentration.

Table 12. Freezing-Point Depression

Rabbit No.	Date	Body weight (g)	Total water volume (cc)	Time (hr/min)	δ
46	21 Oct 1925	2090	700	3.47	-0.60°C
47	21 Oct 1925	2185	630	3.35	-0.61°C
48	22 Oct 1925	2235	660	3.10	-0.60°C

g) Hemoglobin and blood corpuscles

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In five experiments hemoglobin content and red blood-corpuscle count was determined three times in each experiment. Both decreased gradually with intoxication, until finally the former decreased on the average about 21.4 percent (between 16.7 percent and 25.3 percent) and the latter an average of about 20.4 percent (between 13.8 percent and 29.7 percent). In individual cases, however, the decrease in hemoglobin content did not always parallel that of the red count, although a rough approximation existed in all experiments, as is evident from Table 13.

Table 13. Hemoglobin and Blood Corpuscles

Rabbit No.	Hemoglobin				Red blood-corpuscle count (millions)				Leucocyte count (thousands)		
	Be-fore (%)	Midway (%) (hr/min)	After (%)	De-crease (%)	Be-fore	Midway	After	De-crease (%)	Be-fore	Midway	After
33	79	67 (1.20)	59	25.3	7.056	5.336	4.952	29.7	11.0	14.6	13.1
34	72	66 (2.45)	62	16.7	6.208	4.944	4.848	21.9	5.7	10.5	8.7
35	79	77 (2.10)	64	19.0	6.440	6.168	5.432	15.7	8.7	12.3	10.7
36	76	72 (2.30)	59	22.4	6.736	5.734	5.312	21.1	8.5	19.3	29.1
37	80	68 (2.30)	61	23.7	5.348	5.048	4.608	13.8	11.4	13.4	11.1
Mean				21.4				20.4			

cases, however, leucocyte count was considerably higher with the onset of cramps than before the experiment.

Table 14. Leucocyte Count and Types

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Rabbit No.	63			64			65			66			67		
Time (hr/min)	Before	1.40	After	Before	1.40	After	Before	1.40	After	Before	1.40	After	Before	1.40	After
Leucocytes (thousands)	8.7	46.7	16.0	7.9	11.3	9.8	9.7	15.0	9.8	9.5	23.0	18.8	9.2	17.6	15.1
Pseudoeosinophils (%)	55.2	77.6	76.8	40.4	65.6	50.8	42.4	66.0	70.9	43.2	62.0	62.8	46.8	66.4	67.6
(absolute count)	(4.8)	(36.2)	(12.7)	(2.7)	(7.4)	(5.0)	(4.1)	(10.6)	(6.9)	(4.1)	(14.5)	(11.8)	(4.3)	(11.7)	(10.2)
Eosinophils (%)	0.4	0.4	0.8	—	0.8	—	0.8	—	0.4	0.4	0.4	—	0.8	0.4	1.2
Basophils (%)	—	—	0.4	—	—	—	0.4	—	0.4	0.4	—	0.4	0.8	—	—
Lymphocytes (%)	43.6	21.2	21.6	58.4	33.2	48.8	56.4	33.2	29.2	55.2	37.6	36.4	51.6	32.4	31.2
(absolute count)	(3.8)	(9.9)	(3.6)	(4.6)	(3.8)	(4.7)	(5.5)	(5.3)	(2.9)	(5.2)	(8.6)	(6.8)	(4.7)	(5.7)	(4.7)
Large mononuclear leucocytes and transition cells (%)	0.8	0.8	0.4	1.2	0.4	0.4	—	0.8	0.4	0.8	—	0.4	—	0.8	—

In normal rabbits the majority of individual leucocyte cell-types were lymphocytes and pseudoeosinophils, with the former somewhat more numerous than the latter. The pseudoeosinophils increased chiefly at the onset of leucocytosis, while the lymphocytes increased only relatively slightly, so that the percentage of the former was greater during intoxication. With the onset of cramps the lymphocytes decreased almost to the same absolute count as before the experiment, so that an almost equal percentage of the two cell types appeared in the middle period. As for the rest, the number of eosinophils, basophils, large mononuclear leucocytes and transition cells did not change substantially from normal in the intoxication period.

h) Summary

From the complete results of the blood investigations in water intoxication it appears that the decrease in inorganic salt content, blood protein, hemoglobin and red count was very considerable, as is briefly summarized in the following table. The figures in the table indicate percentage decrease in mean value.

NaCl	Na	K	Ca	Mg	P	Protein	Hemoglobin	Red blood-corpuses
22.5	17.3	18.4	19.2	38.3	21.2	23.5	21.4	20.4

Analyzing the table, it may be said in general that all the substances decreased about 20 percent. Since the albumin-globulin ratio underwent no appreciable change, the decrease in blood-protein content must thus be attributed to essential hydremia. Solid matter decreased on the average about 14.6 percent. Residual nitrogen also decreased slightly. Molecular concentration of the serum decreased sharply or, expressed in other terms, the freezing-point depression increased about 0.14°C. Blood-sugar level rose somewhat, without appearance of glycosuria. In so doing, severe leucocytosis (chiefly consisting of pseudoeosinophils) occurred. We may surmise that the causative mechanism of the leucocytosis in water intoxication perhaps originates in the same way as the leucocytosis discovered by Ido in hemorrhagic anemia experiments occurring immediately after venesection. This phenomenon, however, has not yet been completely clarified.

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4. Tissue Research in Water Intoxication

At the end of the experiment the animals were bled to death via carotid section, and the water, solid-matter and sodium-chloride content of the various freshly removed tissues determined. The corresponding tissues of normal rabbits not subjected to water intoxication were used as controls. The tissues for the investigation were prepared from cerebrum, lungs, cardiac muscle, liver, spleen, kidneys, testicles and skeleton muscle.

a) Water content and solid matter

Cerebrum: A small piece of frontal lobe (approx. 1-2 g), without regard to white and gray matter, was used. Solid matter in control animals averaged 20.3 percent (19.2-21.1 percent), while the average in experimental animals was 18.7 percent (17.8-19.5 percent). Accordingly, mean cerebral water content was 79.7 percent in control and 81.3 percent in experimental animals. Details appear in Table 15.

Table 15. Cerebrum

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	Control						Water Intoxication					
Rabbit No.	33	42	43	44	45	Mean	29	30	31	32	33	Mean
Body weight (g)	2550	2210	2095	2150	1930		2045	2675	2300	2190	2100	
Sample weight (g)	1.3185	1.7039	1.4112	1.2934	1.7040		1.4532	2.8276	1.1513	1.5842	1.3212	
Solid-matter weight (g)	0.2539	0.3524	0.2809	0.2677	0.3580		0.2779	0.5519	0.2048	0.2903	0.2484	
Solid matter (%)	19.2	20.7	19.9	20.6	21.1	20.3	19.1	19.5	17.8	18.3	18.8	18.7

Lungs: A small piece of the left inferior lobe (approx. 1-2 g) was used in the experiment. Vascular section was thus avoided as much as possible. Solid matter of the lungs averaged 20.6 percent (20.2-20.9 percent) in control and 18.6 percent (18.0-19.9 percent) in experimental animals. Correspondingly, water content was 79.4 percent in the former and 81.4 percent in the latter. Individual results are compiled in Table 16.

Table 16. Lungs

	Control						Water Intoxication					
Rabbit No.	58	59	60	61	62	Mean	63	64	65	66	67	Mean
Body weight (g)	1970	2370	1930	2080	2100		2230	2450	2170	2270	2150	
Whole organ (g)	l. 2.9	3.8	3.3	3.2	3.4		4.6	6.2	2.1	4.8	4.4	
	r. 4.1	5.3	4.5	4.6	4.7		6.1	8.5	5.7	5.5	5.6	
Sample weight (g)	1.0128	1.7954	1.5680	1.3992	1.4695		1.1298	1.4935	1.5361	2.3393	1.6202	
Solid-matter weight (g)	0.2115	0.3630	0.3257	0.2848	0.3011		0.2035	0.2783	0.3047	0.4232	0.2932	
Solid matter (%)	20.9	20.2	20.8	20.4	20.5	20.6	18.0	18.6	19.9	18.1	18.4	18.6

Cardiac muscle: A piece of the apex (approx. 1-2 g) was resected for the investigation. Solid matter averaged 20.2 percent (19.3-20.6 percent) in control and 18.6 percent (18.1-18.9 percent) in experimental animals. Accordingly, water content was 79.8 percent in the former and 81.4 percent in the latter, as is evident from Table 17.

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Table 17. Cardiac Muscle

	Control						Water Intoxication					
Rabbit No.	58	59	60	61	62	Mean	63	64	65	66	67	Mean
Whole organ (g)	4.6	6.8	5.4	4.7	5.0		5.3	6.2	5.3	5.3	5.1	
Sample weight (g)	1.0208	1.8243	1.1424	1.2624	1.3211		1.1826	1.0543	2.0950	1.9311	1.6430	
Solid-matter weight (g)	0.1984	0.3708	0.2358	0.2500	0.2689		0.2150	0.1982	0.3937	0.3650	0.3050	
Solid matter (%)	19.3	20.3	20.6	20.5	20.4	20.2	18.1	18.8	18.8	18.9	18.6	18.6

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Skeleton muscle: A small piece (approx. 1-2 g) of the left ilio-psoas was used in the experiment. Solid matter averaged 21.0 percent (20.0-22.5 percent) in control and 18.2 percent (16.6-20.4 percent) in experimental animals. Accordingly, mean water content was 79.0 percent in the former and 81.8 percent in the latter, as is shown in Table 18.

Table 18. Skeleton Muscle

Rabbit No.	Control							Water Intoxication						
	22	38	42	43	44	45	Mean	15	16	18	19	20	21	Mean
Body weight (g)	2180	2550	2210	2095	2150	1900		2335	2800	2415	2040	3025	2400	
Sample weight (g)	0.9445	2.4649	1.9421	1.4568	1.3136	2.3202		1.3212	1.6076	0.8379	1.3333	1.1109	1.6366	
Solid-matter weight (g)	0.1946	0.4906	0.4059	0.3758	0.2635	0.6222		0.2219	0.3151	0.1706	0.2263	0.2061	0.2707	
Solid matter (%)	20.5	20.0	20.9	21.0	20.9	22.5	21.0	17.4	18.9	20.4	17.3	18.6	16.6	18.2

Liver: The small piece (approx. 2-3 g) used in the determination was resected from the peripheral section adjacent to the anterior abdominal wall. Solid matter averaged 26.7 percent (25.1-28.3 percent) in control and 23.0 percent (21.2-24.9 percent) in experimental animals. Mean water content was thus 73.3 percent and 77.0 percent respectively. Complete results are tabulated below.

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Table 19. Liver

Rabbit No.	Control							Water Intoxication						
	22	38	42	43	44	45	Mean	15	16	18	19	20	21	Mean
Whole organ (g)	59	74	62	56	58	60.5		64.5	80.5	61	61	68	75	
Sample weight (g)	3.0655	2.8107	2.6864	2.1362	2.5051	2.4854		2.1605	3.0259	3.2593	3.0699	3.0993	2.6297	
Solid-matter weight (g)	0.8770	0.7646	0.6776	0.5768	0.6293	0.6589		0.5497	0.6679	0.7234	0.6519	0.7250	0.6137	
Solid matter (%)	28.3	27.1	26.2	27.0	25.1	26.4	26.7	24.9	22.1	22.3	21.2	23.3	24.3	23.0

Spleen: The whole organ was used for determination, and the fibrous portion carefully excised. Solid matter averaged 21.0 percent (20.5-21.7 percent) in the control and 19.7 percent (19.1-20.1 percent) in the experimental animals. Mean water content was 79.0 percent and 80.3 percent respectively, as is evident from Table 20.

Table 20. Spleen

Rabbit No.	Control							Water Intoxication						
	22	38	42	43	44	45	Mean	15	16	18	19	20	21	Mean
Whole organ (g)	0.7614	1.0333	0.9120	0.9611	0.9715	1.0632		0.6425	0.7341	0.7020	0.9616	1.0623	1.7265	
Solid-matter weight (g)	0.1653	0.2124	0.1921	0.2009	0.1938	0.2258		0.1253	0.1405	0.1389	0.1999	0.2607	0.3255	
Solid matter (%)	21.7	20.6	21.1	20.9	20.5	21.0	21.0	20.1	19.1	19.8	19.8	19.7	19.6	19.7

Kidneys: A small piece (approx. 1-2 g) of the cortex of the left kidney was used in the experiment, to avoid medullary section as much as possible. Solid matter averaged 22.9 percent (22.2-24.1 percent) in the control and 21.4 percent (20.6-22.0 percent) in the experimental animals. Water content was 77.1 percent in the former and 78.6 percent in the latter. Complete results are given in Table 21.

Table 21. Kidneys

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Rabbit No.	Control							Water Intoxication						
	22	38	42	43	44	45	Mean	15	16	18	19	20	21	Mean
Whole organ (g)	5.8	9.0	6.0	5.3	5.5	5.5		7.5	8.0	7.3	6.5	8.0	7.8	
	5.8	9.0	6.0	5.3	5.5	5.5		7.5	8.0	7.3	6.5	8.0	7.8	
Sample weight (g)	0.8606	1.9589	1.3051	1.2521	1.1744	1.3408		0.6394	1.0515	1.1118	1.3372	1.3277	0.7409	
Solid-matter weight (g)	0.2389	0.4450	0.2923	0.2939	0.2696	0.2694		0.1149	0.2202	0.2349	0.2936	0.2577	0.1644	
Solid matter (%)	24.1	22.3	22.4	23.4	23.0	22.2	22.9	21.3	20.6	21.9	22.0	21.7	20.8	21.4

Testicles: Half of the left testicle was used in the experiment and the epididymis was removed. Solid matter averaged 15.2 percent (14.3-16.4 percent) in control and 12.4 percent (10.4-14.1 percent) in experimental animals. Mean water content was 84.8 percent and 87.6 percent respectively, as is shown in Table 22.

When all the results obtained in this portion of the experiment were analyzed, the percentage decrease in solid matter in the tissues used in determination was greatest in the testicles, while the percentage increase in water content was greatest in the liver.

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Table 22. Testicles

	Control						Water Intoxication					
Rabbit No.	58	59	60	61	62	Mean	63	64	65	66	67	Mean
Whole organ (g)	2.6	3.5	2.0	3.3	2.7		4.9	3.3	2.9	2.3	2.6	
	2.6	3.4	2.2	3.6	2.7		5.1	3.2	2.8	2.3	2.6	
Sample weight (g)	1.3129	1.5337	1.2433	1.5042	1.3152		1.3462	1.6121	2.4738	1.7950	1.4111	
Solid-matter weight (g)	0.1952	0.2510	0.1901	0.2294	0.1876		0.1643	0.2280	0.2574	0.2244	0.1821	
Solid matter (%)	14.9	16.4	15.3	15.3	14.3	15.2	12.2	14.1	10.4	12.5	12.9	12.4

b) Sodium-chloride content

The tissue used in solid-matter investigation was again ground fine in the mortar and the sodium-chloride content determined. It was taken as the average of two to three determinations in all tissues except the spleen, where, due to the small size of the organ, it was only determined once. Complete results are given in Table 23.

Rather large individual differences occurred in cerebral sodium-chloride content even in the control animals. It averaged 47.4 mg/percent (34.2-68.6 mg/percent), while the mean in intoxication experiments was 36.7 mg/percent (25.6-42.0 mg/percent). Sodium-chloride content thus decreased about 23 percent in water intoxication. In the lungs mean sodium-chloride content was 97.8 percent (81.0-111.7 mg/percent) in the control and 69.8 mg/percent (60.8-77.8 mg/percent) in the intoxication experiments. It therefore decreased about 29 percent in water intoxication. Cardiac-muscle mean was 41.6 mg/percent (35.4-51.1 mg/percent) in controls and 27.2 mg/percent (23.1-30.9 mg/percent) experimentally. Percentage decrease for this tissue was thus 35 percent. Individual differences in sodium-chloride content in the skeleton muscle were relatively small. Here the mean was 25.3 mg/percent (20.5-27.4 mg/percent) in the control and 12.3 mg/percent (9.2-15.3 mg/percent) in the actual experiments. It therefore decreased about 51 percent in water intoxication. It should be emphasized here that the decrease in sodium chloride was greatest in the skeleton muscle, where it was reduced by half. At the same time the liver sodium-chloride content did not decrease, but rather increased somewhat, since it averaged 19.5 mg/percent (18.3-24.6

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Table 23. Tissue Sodium-Chloride Content (mg/percent)

	Cerebrum				Lungs				Cardiac Muscle				Skeleton Muscle			
	Control		W. I.		Control		W. I.		Control		W. I.		Control		W. I.	
	Rabbit No.	NaCl	Rabbit No.	NaCl	Rabbit No.	NaCl	Rabbit No.	NaCl	Rabbit No.	NaCl	Rabbit No.	NaCl	Rabbit No.	NaCl	Rabbit No.	NaCl
	38	34.4	23	42.0	58	117.3	63	77.8	58	51.1	63	30.2	22	20.5	15	13.1
	42	34.2	30	38.8	59	88.1	64	68.3	59	37.1	64	23.3	38	26.2	16	13.4
	43	48.0	31	25.6	60	109.9	65	68.5	60	35.4	65	23.1	42	27.0	18	11.4
	44	51.7	32	40.1	61	81.0	66	60.8	61	46.7	66	25.3	43	23.7	19	9.2
	45	68.6	33	36.8	68	97.2	67	73.6	62	37.5	67	30.9	44	27.4	20	11.5
													45	27.2	21	15.3
Mean	47.4		36.7		97.8		69.8		41.6		27.2		25.3		12.3	
Percentage variation	- 22.6%				- 28.6%				- 34.6%				- 51.4%			

	Liver				Spleen				Kidneys				Testicles			
	Control		W. I.		Control		W. I.		Control		W. I.		Control		W. I.	
	Rabbit No.	NaCl	Rabbit No.	NaCl	Rabbit No.	NaCl	Rabbit No.	NaCl	Rabbit No.	NaCl	Rabbit No.	NaCl	Rabbit No.	NaCl	Rabbit No.	NaCl
	22	20.4	15	23.0	22	28.6	15	47.8	22	43.4	15	39.4	58	74.9	63	48.3
	38	23.3	16	20.1	38	34.0	16	22.5	38	52.6	16	37.9	59	73.6	64	68.5
	42	21.2	18	18.5	42	38.2	18	21.6	42	54.7	18	31.1	60	65.8	65	40.7
	43	19.2	19	18.9	43	33.9	19	24.4	43	49.6	19	40.0	61	83.5	66	43.9
	44	18.3	20	24.4	44	49.4	20	23.0	44	54.3	20	33.4	62	63.8	67	54.3
	45	24.6	21	24.1	45	30.2	21	16.1	45	52.4	21	54.4				
Mean	19.5		21.6		35.3		25.9		51.2		39.0		72.3		51.1	
Percentage variation	+ 10.8%				- 26.6%				- 23.8%				- 29.3%			

mg/percent) in control and 21.6 mg/percent (18.5-24.4 mg/percent) in experimental livers. Sodium-chloride content of the organ thus increased about 11 percent in water intoxication. Of all the tissues investigated, the liver was the only organ whose sodium-chloride content increased in intoxication. From experimental determinations it is found that sodium-chloride content in the liver, as in skeleton muscle, was far lower. In the spleen it averaged 35.3 mg/percent (28.6-49.4 mg/percent) in control and 25.9 mg/percent (16.1-47.8 mg/percent) in intoxication experiments. It therefore decreased about 27 percent in the latter. In the kidneys it averaged 51.2 mg/percent (43.4-54.7 mg/percent) in control and 49.0 mg/percent (31.1-52.4 mg/percent) in intoxication experiments. The decrease in water intoxication was thus 24 percent. In the testicles it averaged 72.3 mg/percent (63.8-83.5 mg/percent) in control and 51.1 mg/percent (40.7-68.5 mg/percent) in intoxication experiments, thus decreasing about 29 percent in water intoxication.

c) Summary

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All the results obtained in tissue investigations are grouped in brief in the following table. Figures in the table show percentage increase (+) or decrease (-) in mean value in comparison with the control value.

	Cerebrum	Lungs	Cardiac muscle	Skeleton muscle	Liver	Spleen	Kidneys	Testicles
Water content	+ 2.01	+ 2.52	+ 2.02	+ 3.81	+ 5.05	+ 1.66	+ 2.95	+ 3.30
Solid matter	- 7.88	- 9.71	- .792	-13.6	-13.9	- 6.15	- 6.55	-18.4
Sodium chloride	-22.6	-28.6	-34.6	-51.4	+10.8	-26.6	-23.8	-29.3

As is evident from the table, water content increased in all tissues investigated, while solid matter correspondingly decreased. It is worth noting that water increased most in the liver, while solid matter decreased most in the testicles and somewhat less in the liver and skeleton muscle, though still very sharply. Sodium-chloride content decreased very sharply in all tissues except those of the liver, especially in the skeleton and in the cardiac muscle. It seems very interesting that sodium-chloride content increased solely in the liver, although even this increase was slight. Since liver sodium-chloride content varied between 18.3 and 24.6 mg/percent (mean 19.5 mg/percent) in control animals and between 18.5 and 24.4 mg/percent (mean 21.6 mg/percent) in experimental animals, one can either say that there was no important change in water intoxication (if its variability range along is considered), or that there was a slight increase (if the mean value alone is considered). In any case, it is certain that sodium-chloride content in the liver, at least, did not decrease in water intoxication. Therefore it can be seen that sodium-chloride metabolism in the liver differed from that in the other tissues in water intoxication. Further investigations may determine the reason why the sodium-chloride content increased only in the liver, and why it decreased most sharply in the skeleton muscle.

5. Urine Investigations in Water Intoxication

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The urinary bladder was completely evacuated by catheter just before the experiment. All the urine was carefully collected at half-hourly intervals thereafter until the onset of cramps and utilized in the investigation. The urine collected within 4-5 hr from animals to be used in the experiment a few days later was analyzed in the same way, as controls.

The time period during which control-experiment urine was collected was therefore somewhat longer than in water intoxication, as may be seen in Table 25.

a) Urine volume and specific gravity

Diuresis was progressive as the water intoxication period lengthened, and urine evacuation was especially copious 2.5-3 hr after the beginning of the experiment. Specific gravity of the urine generally decreased inversely as the urine volume secreted, but without strict regularity, as is shown in Table 24.

Table 24. Urine Volume, Specific Gravity and Sodium-Chloride Secretion During Intoxication Up to the Onset of Cramps

Rabbit No. 21	Time (hr/min)	1.30	2.40	3.27	
	Urine volume (cc)	29	95	100	
	Specific gravity	1003	1006	1005	
	NaCl (mg)	21.85	95.29	88.42	
23	Time (hr/min)	1.5	2.5	3.5	3.33
	Urine volume (cc)	10	55	110	55
	Specific gravity	1007	1004	1007	1008
	NaCl (mg)	3.3	19.25	84.7	42.35
29	Time (hr/min)	1.5	2.5	2.35	4.20
	Urine volume (cc)	55	95	130	56
	Specific gravity	1007	1005	1003	1004
	NaCl (mg)	20.9	52.25	9.1	37.5

The ratio of urine secreted to water ingested during the experimental period varied widely in individual experiments. The proportion of the former relative to the latter averaged 25 percent (14-37 percent), as is evident from Table 25.

b) Inorganic salts

Sodium chloride was determined according to Rusznyak, sodium, potassium, calcium and magnesium according to Kramer-Tisdall and phosphorus according to Bell-Doisy. While the individual inorganic salts in the blood decreased almost equally sharply in each experiment, this was not the case with urine, as we shall see. The results are summarized in Table 25.

Sodium chloride: In the control urine the quantity of sodium chloride secreted averaged 12.4 mg (2.6-12 mg, and, in one case, 43 mg), while in the intoxication urine, the mean was 138 mg (50-213 mg). It

Table 25. Urinalysis

	Rabbit No.	Body weight (g)	Total water volume (cc)	Time (hr/min)	Urine volume (cc)	$\frac{U}{W} \times 100$	NaCl mg	Na mg	K mg	Ca mg	Mg mg	P mg	Total N (mg)
Control	15			4.20	12		10.81	4.14	42.1	2.00	2.40	3.30	60
	23			4.5	14		2.56	1.86	87.2	1.22	3.05	4.00	87
	34			4.40	15		3.75	15.22	75.8	1.10	11.08	6.00	117
	35			4.30	11		11.55	3.00	60.1	1.60	3.29	5.08	37
	36			4.35	25		42.75	9.3	27.3	5.80	2.12	2.53	134
	37			4.40	10		11.9	3.33	70.7	1.73	1.82	3.75	121
	40			4.15	15		3.60	1.41	39.2	1.50	2.12	5.09	99
	Mean						12.42	5.47	57.4	2.12	3.83	4.28	94
Water Intoxication	21	2400	840	3.27	224	23	205.4	51.0	26.0	11.2	5.42	9.4	448
	23	2200	770	3.33	230	30	149.6	84.2	60.0	7.1	5.64	25.5	439
	29	2045	900	4.20	330	37	201.7	60.3	39.8	9.5	4.13	21.1	376
	34	2000	800	4.55	210	23	123.9	13.2	41.8	10.8	3.05	22.1	494
	35	2035	900	4.12	305	34	104.3	21.7	40.0	17.7	5.31	14.2	500
	36	2050	720	4.3	107	15	49.9	11.2	41.7	5.0	1.66	13.2	142
	37	2150	945	4.15	128	14	57.6	10.9	7.3	4.0	2.73	4.3	195
	40	2040	700	3.23	115	16	212.8	30.3	5.6	6.2	1.00	31.4	222
	Mean					25	138.2	35.5	33.0	9.8	3.62	17.7	352
	Quotient of mean to control-urine mean						11.1	6.49	0.575	4.62	0.945	4.14	3.74

thus appears that sodium-chloride secretion in the latter was more plentiful than in the control urine, i.e., 11.1 times more. It should be emphasized that sodium-chloride secretion in the urine was greatest of all inorganic salts in absolute quantity, as well as in proportion to the control-urine volume.

Sodium: The quantity of sodium secreted in the urine averaged 5.47 mg (1.41-15.22 mg) in the control and 35.5 mg (10.9-84.2 mg) in the intoxication urine. Sodium volume in the latter was thus 6.49 times as great as in the former.

Potassium: In contrast to the other inorganic salts, the quantity of potassium secreted in the experimental urine decreased, with the exception of one case (Rabbit No. 36) in which it increased somewhat. Mean was 57.4 mg (27.3-87.2 mg) in control and 33.0 mg (5.6-60.0 mg) in experimental urine. Potassium secretion was therefore about half as great as in control urine.

Calcium: Volume of calcium secreted averaged 2.1 mg (1.1-5.3 mg) in control and 9.8 mg (4.0-17.7 mg) in intoxication urine; the latter was 4.6 times as great as the former.

Magnesium: Average amount of magnesium secreted was 3.83 mg (1.82-11.98 mg) in the control and 3.62 mg (1.0-5.64 mg) in the intoxication urine. Magnesium secretion thus remained almost unaltered.

Phosphorus: Average volume of inorganic phosphorus was 4.28 mg (2.53-6.00 mg) in control and 17.7 mg (4.3-31.4 mg) in experimental urine. The latter was therefore 4.14 times as great as the former.

c) Sodium-chloride secretion per unit time

It is necessary to pursue sodium-chloride secretion per unit time, since this salt was secreted far more abundantly than others and also plays an important part in material exchange. Sodium-chloride secretion, like its volume, increases gradually with intoxication. Details may be noted in Table 24.

d) Total nitrogen

The quantity of total nitrogen secreted averaged 94 mg (37-134 mg) in control and 352 mg (142-500 mg) in intoxication urine; the latter was thus 3.7 times as great as the former, as may be seen from Table 25.

e) Urine investigations in the recovery period

To understand how secretion of these substances behaves during the period of recovery from water intoxication, I also made chemical determinations of their presence in the urine during this time. The urine was collected in portions and utilized in chemical analysis. The following table illustrates the results thus obtained. It may be noted in Table 26 that diuresis still persisted several hours after the onset of cramps. Urine volume secreted within 13 hr of the inception of the experiment reached 88 percent and that secreted within 26 hr reached 94 percent of the total water ingested. If extrarenal water secretion through diarrhea, salivation, respiration, etc., is considered, it is certain that the water ingested in about 24 hr was almost completely eliminated. Secretion of the inorganic salts and total nitrogen in the recovery period was the exact opposite of that during intoxication. Indeed the inorganic salts such as sodium chloride, sodium, calcium, phosphorus and total nitrogen were secreted gradually, during recovery, in greatly decreased quantity, while potassium, on the contrary, was gradually eliminated in an increased amount.

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f) Summary

If one considers the results of the urine investigations in toto, it is found that diuresis became progressively more pronounced with time. Total urine volume secreted prior to the onset of cramps attained an average of approximately one-fourth of the water ingested. Urine volume

Table 26. Urinalysis During Recovery Period (Rabbit No. 36)

Exp. inception 11 a.m. 10 Sept 1925. Cramps set in toward 3:33:	Urine vol- ume	Spe- cific grav- ity	NaCl	Na	K	Ca	Mg	P	Total N
11 a.m.—2:33 p.m.	230	1005	140.6	84.2	60.0	7.1	5.64	25.5	439
2:33 p.m.—4:10 p.m.	125	1005	111.8	20.1	9.3	3.38	1.81	11.9	390
4:10 p.m.—midnight	320	1007	141.	35.8	71.7	7.04	1.86	38.7	358
0:00 a.m.—1 p.m. 11 Sept	50	1021	0.5	trace	174.	12.55	2.20	10.6	457

secreted in the recovery period of about 24 hr was approximately as great as that of the water ingested. Individual inorganic salt and total nitrogen secretions are once more briefly summarized in the following table. Figures in the table indicate average quotients of the quantities of the substances concerned in the experimental compared with the control urine.

NaCl	Na	K	Ca	Mg	P	Total N
11.1	6.5	0.58	4.6	0.95	4.1	3.7

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As is evident from the table, secreted volume of sodium chloride, sodium, calcium, phosphorus and of total nitrogen was far greater in the experimental urine than in the controls. Above all, the quantity of sodium chloride was far greater in the former than in the latter. Magnesium was almost unchanged. Potassium decreased greatly. Sodium-chloride secretion per unit time increased gradually with intoxication. Secretion of this substance was just the reverse during the recovery period.

6. Body Temperature and Body Weight

Body temperature fell gradually with intoxication, until in the last phase, in which cramps set in, it was approx. 2°C (1.6°-2.5°C) lower than before the experiment, as may be seen from Table 27.

Body weight increased gradually corresponding to the quantity of water ingested. In so doing, extrarenal secretion of water must have been very slight, since the difference between increase in body weight and quantity of water ingested was almost exactly identical with the volume of urine evacuated in the meantime. The urine secreted up to the onset of cramps was not more than about one-fourth of the water ingested, and, consequently, most of the water was thus retained in the body.

Table 27. Body Temperature

Rabbit No.	Before experiment	Midway (hr/min)	At onset of cramps
6	39.3°C	38.2°(0.10)37.9°(2.5)	37.0°(3.5)
7	39.4°C	38.7°(0.35)38.7°(1.45)37.4°(3.15)	36.9°(4.47)
8	36.5°C	35.9°(1.10)35.4°(2.35)	34.6°(3.54)
12	38.35°C	38.15°(0.30)37.7°(1.30)37.5°(2.0)37.5°(2.40)	36.75°(3.10)
18	38.9°C	38.0°(1.10)37.8°(1.40)37.2°(2.40)	36.4°(3.10)

7. Hemolysis in Water Intoxication Deaths

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Further administration of water after cramps had occurred caused death to ensue more or less quickly, as Rowntree had already reported. In such cases it was discovered, incidentally, that hemolysis appeared. On the basis of this discovery, further experiments were performed. This was done in the same way as before, continuing to administer approx. 0.5 cc of water each time after the onset of cramps. Blood was taken off in Wright's capillary every half hour until death. Four such experiments showed that in all cases hemolysis in the serum increased intensively with time, as could be judged from the reddish hue of the serum. The animals were dissected immediately after death and it was ascertained that hemoglobinuria had already occurred in the urinary bladder in three out of four experiments. Therefore, it is very likely that the hemoglobin leaves the red blood-corpuscles if, after hydremia takes place with water intoxication, the blood is thinned to the point that the water-salt balance between the red blood-corpuscles and the exterior medium is disturbed. It is still not certain, however, whether the hemolysis is a direct cause of death or only a symptom of water intoxication. In any case, it is interesting that hemolysis appears in water intoxication deaths.

8. Summary and Conclusions

All the experimental water-intoxication results described above are summarized as follows.

- (1) Solid matter in the blood decreased about 15 percent.
- (2) Inorganic salts, such as NaCl, Na, K, Ca and Mg in the serum and P in plasma, decreased about 20 percent.

- (3) Blood protein decreased about 23.5 percent. Albumin-globulin ratio showed no perceptible change.
- (4) Residual nitrogen decreased slightly.
- (5) Blood-sugar level increased by degrees with the progress of intoxication, without occurrence of glycosuria.
- (6) Hemoglobin content and red blood-corpuscle count decreased gradually, until ultimately the former was about 21.4 percent less and the latter about 20.4 percent less.
- (7) Decrease in hemoglobin content and red blood-corpuscle count always went hand in hand with increase in blood sugar. /382
- (8) A considerable leucocytosis occurred, reaching its maximum value not at the end but in the development of water intoxication. Leucocytosis consisted chiefly of pseudoeosinophilia.
- (9) Molecular concentration of the serum decreased sharply. Freezing-point depression increased about 0.14°C .
- (10) Water content in all tissues examined (cerebrum, lungs, cardiac muscle, skeleton muscle, liver, spleen, kidneys and testicles) increased; their solid matter decreased correspondingly.
- (11) Sodium-chloride content decreased sharply in all tissues except the liver, with the decrease most in the skeleton muscle. On the other hand, its content in the liver increased slightly.
- (12) Diuresis increased with time. Total urine volume up to the onset of cramps was about one-fourth of the water ingested. Total water ingested was not eliminated for about 24 hr.
- (13) Experimental urine, when compared with control urine, showed far more abundant secretion of inorganic salts such as NaCl (11 times), Na (6.5 times), Ca (4.5 times), and P (4 times). In contrast, potassium alone decreased by half, while magnesium remained almost unchanged.
- (14) Sodium-chloride secretion per unit time increased with the progress of intoxication.
- (15) Total nitrogen secreted in the urine was about four times as great as in control urine.
- (16) In water intoxication, equilibrium disturbances in the body must exist both in inorganic salts and in nitrogen compounds.
- (17) Secretion of inorganic salts and total nitrogen was directly inverse during the period of recovery from water intoxication.
- (18) Body temperature fell gradually until it was about 2°C lower with the onset of cramps.
- (19) Water ingestion correspondingly increased body weight significantly.
- (20) Further administration of water after the onset of death caused death, with the appearance of hemolysis.

In conclusion, it is my duty and pleasure to express my heartfelt thanks to Professor Inada for stimulating this research and providing energetic, clear-sighted guidance.

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